Pharmacokinetic-Pharmacodynamic (PK-PD) Modeling: A Review
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Abstract
The term pharmacokinetic and pharmacodynamic (PK/PD) modeling refers to a data driven exploratory analysis based on a mathematical/statistical model. A model cannot be fully pre-specified prior to experiment and may be developed or further refined depending on the results. A mechanistic model is one in which parameters correspond to physical entities in the subject matter of the model whilst an empirical model is without such mechanistic elements. Additional definitions include a descriptive model which is a priori applicable only to a restricted set of circumstances (patients, designs etc) and a predictive model that explicitly incorporates variables quantifying important design and baseline features so that the model can predict outcomes conditional upon arbitrary values of those variables. Science of modeling is data driven and it relies on multiple analyses of the same data-set in an iterative mode with successive and/or competing models.

Due to rising costs and reduced productivity of drug development there is a growing interest in use of alternative methods to stimulate development of new drugs. The Pharmacodynamic/pharmacokinetic (PK/PD) modeling and simulations can be used as an ‘applied science’ tool to provide answers on efficacy and safety of new drugs faster and at a lower cost.

INTRODUCTION
The birth of pharmacokinetic-pharmacodynamic (PK/PD): In the late 60’s a premature birth due to presence of a delay between norepinephrine concentration-time profiles and the kinetics of pharmacological response, i.e. blood pressure-time data leads to introduced the concept of a “hypothetical effect compartment” by Gino Segre to account for this delay [1]. This allowed an empirical description of time-dissociated kinetics. Lewis Sheiner and coworkers were made Segre’s model more popular. They were the first to formalize this concept into a model to describe hysteresis caused by distribution to the biophase and it was reborn as the —Link Model [2].

The primary objective of pharmacokinetic-pharmacodynamic (PK-PD) modeling is prediction of the time course of the drug effect intensity in vivo in health and disease [3]. PK-PD modeling has become a key success factor in drug discovery and development. PK-PD modeling is widely used as the theoretical basis for optimization of the dosing regimen and the delivery profile of new (and existing) drugs in Phase II clinical trials. Moreover, the use of PK-PD modeling for optimization of the design of Phase II clinical trials, using clinical trials simulation has become well established [3, 4].

In recent years, PK-PD modeling has been increasingly applied in drug discovery and early drug development. Within this context, PK-PD modeling constitutes the theoretical basis for (a) the selection of drug candidates, (b) lead optimization, and (c) the optimization of early proof-of-concept clinical trials on the basis of information from preclinical studies.

The applications of PK-PD modeling described above rely on the prediction, in a strictly quantitative manner, of the PK-PD properties of novel drugs in man using prior information from in vitro bioassays, in vivo animal studies, or early clinical studies in man. Not surprisingly, PK-PD modeling has developed from an empirical and descriptive approach into a scientific discipline based on the patho-physiological mechanisms behind PK-PD relationships. It is now well accepted that mechanism based PK-PD models have much improved properties for extrapolation and...
prediction. A pertinent feature of mechanism-based PK-PD models is that they contain specific expressions to characterize processes on the causal path between drug administration and effect, thereby relying on relevant biomarker data [5]. This includes (a) target site distribution, (b) target binding and activation, (c) pharmacodynamic interactions, (d) transduction, (e) homeostatic feedback mechanisms, and ultimately, (f) the effects of the drug on disease processes and disease progression.

A key element in mechanism-based PK-PD modeling is the explicit distinction between parameters to describe (a) drug-specific properties and (b) biological system specific properties. Drug-specific parameters describe the interaction between the drug and the biological system in terms of target affinity and target activation, whereas system-specific parameters describe the functioning of the biological system. This concerns within-system pharmacodynamic interactions, time-dependent transduction mechanisms, and homeostatic feedback mechanisms.

In this review, disease processes and disease progression are described in terms of biological system-specific parameters. The explicit distinction between drug-specific parameters and biological system specific parameters is crucial to the prediction of in vivo drug effects. It has been demonstrated that drug-specific properties (i.e., receptor affinity, intrinsic efficacy) can often be predicted on basis of in vitro bioassays [6, 7, 8]. Furthermore, the values of drug-specific parameters are identical between species and individuals. This implies that these parameters do not require scaling when they are applied in interspecies extrapolation. Moreover, there is typically no intra- and inter-individual variability in the values of these parameters [7, 8]. In contrast, biological system-specific parameters can only be estimated by in vivo systems analysis. The values of biological system specific parameters can vary between species, individuals, and conditions. This implies that interspecies scaling of biological system-specific parameters may be required [9]. Finally, intra- and inter-individual variation in biological system-specific parameters must be taken into account. In this review, we present an overview of the basic principles and recent developments of mechanism-based PK-PD modeling.

**PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODELING**

Pharmacokinetic/pharmacodynamic (PK/PD) models describe the relationship between plasma and/or tissue drug concentrations and a pharmacological effect usually expressed as a biomarker or surrogate end point. The relationship between dose, plasma concentrations, and pharmacological effects is frequently complex. A quantitative relationship of PD to dose and/or PK is usually of interest, and PD information is frequently collected together with PK information. Ideally, PK/PD relationships should be obtained in individual subjects or patients to understand the sources and magnitude of variability in exposure response. However, in most cases, PK/PD relationships are population based. In addition, clinical efficacy and safety observations may also be available depending on the study design. PK/PD science, mechanistic, and/or empirical models are available to better understand the complex links between dose, PK, and PD. These models may be descriptive and/or predictive of the time course of PD effects [10, 11, 12]. Predictive models, when properly developed, may be used to guide starting doses and regimens (as well as adjustments of dose/dosing regimens in special populations), add evidence to the certainty of the decision to allow market access, and provide a better understanding of outcomes from clinical benefit studies. PK/PD studies are intended to link the dose-PK exposure profile relationship with the pharmacodynamic response; of particular interest is the time course of the pharmacological/pathophysiological effects. It is important to prospectively design PK/PD studies and the intended analysis plan to adequately form the foundation for providing scientifically sound evidence of efficacy or safety of a drug substance. The study design and analysis plan should be informative and appropriately linked to the question or purpose of the study. Attention should be paid to the appropriateness of the PD response and the intended analysis and interpretation of the data.
Basal Conditions

Drug responses are generally measured as a drug induced change from a baseline value in the physiological variable of interest over time ($E_0$). In most cases, the baseline is established by performing several predose measurements of the physiological variable of interest and calculating an average predose value. Establishment of a baseline reference is essential to fully elucidate the effect of the drug. However, it must be recognized that there may be baseline changes of the physiological measure or biomarker due to endogenous cyclical fluctuations (e.g., circadian rhythms) [13], disease-induced changes (progression or remission) [14, 15], and environmental changes such as food intake [16]. The basal condition therefore can be expressed as a function that may be a constant or vary with time according to some physiologically meaningful structural model:

$$E_0 = f(x, t)$$

Where, $E_0$ is the baseline response, and $x$ is the variable defining the change in baseline over time. The value of $x$ may be as simple as an average value or as complex as a cosine function.

Drug Response

Drug response can then be modeled as a drug-induced change from this baseline value.

$$\text{RESPONSE} = E_0 + F(X, \text{EXPOSURE}),$$

Where, $X$ is a vector of parameters describing the relationship between drug exposure and response. During the analysis and modeling phase, the baseline reference measure is often subtracted from the drug-induced response measured at all times of assessment and the difference then modeled. This procedure should be avoided, if possible, since one loses information with regard to the variability in the baseline value. Using the absolute change from baseline may result in an incorrect model of response, obscures the between treatment comparison, and makes the intersubject comparison difficult since there may be considerable variability in the baseline changes among different individuals. Baseline changes in the response variable should be measured whenever possible, using a placebo, and the baseline should be modeled either as a constant value with random error or with an appropriate baseline model [17].

Dose Range

It is very important to choose the appropriate range of drug doses and systemic exposure to be able to assess the important features of the PK/PD relationship. Exposure too low: in some cases, it is not practical to increase drug exposure to the extent that the maximum response can be defined because of limitations posed by adverse events. In this situation, care should be taken to interpolate predictions rather than extrapolate.

Well-designed phase I studies may provide some insight into $E_{\text{max}}$ values for efficacy biomarkers as well as for adverse effects. Exposure too high: If drug exposure consistently produces responses near or at the maximum response, it is not feasible to describe a drug exposure-response relationship. This makes it difficult to determine the smallest dose necessary to achieve the maximum response and often leads to dosing recommendations that are excessive. Modeling the exposure-response relationship is very much dependent on the mechanism of action of the drug. In vitro studies that may elucidate this mechanism are very important in the early stage of drug development.

For example, the drug-induced changes in the physiological variable of interest are often modelled using classical drug receptor theory following the law of mass action. This theory predicts that as receptors in the target organ interact with the drug, the response will increase with increasing interaction until all receptors have been occupied, at which time no further increase will occur. The model is a special case of the general equation presented above and is often called the $E_{\text{max}}$ model after one of its two parameters [17].

$$\text{RESPONSE} = E_0 + \frac{E_{\text{max}} \cdot \text{EXPOSURE}}{E_{50} + \text{EXPOSURE}}.$$
Where, RESPONSE is the physiological response variable of interest, $E_0$ is the response when drug concentration is zero, EXPOSURE is the amount of drug to which the responder is exposed, $E_{\text{max}}$ is maximum change in response that the drug can produce, and $E_{50}$ is the degree of exposure to the drug that produces 50% of $E_{\text{max}}$. The in vivo application of this model, although incorporating solid scientific premises, is generally empirical. This relationship describes a monotonically increasing response that approaches $E_{\text{max}}$ asymptotically at high concentrations. Although this model is frequently used, there are many possible approaches depending on the mechanism of action of the drug. Application of this model is relatively simple under steady state conditions. Non-steady-state conditions require added complexities in the quantification of this relationship but nevertheless may provide valuable additional information [17, 18].

Concentration-Based PK/PD Models

If the drug exposure is known in the form of a complete concentration-time profile, the PK/PD model can relate the concentration provided by the kinetic model to the observed effect. In its simplest form, the observed effect is directly related to the effect site concentration, and the concentrations at the effect site and in plasma are in equilibrium. This is the case at least under pharmacokinetic steady-state conditions for all directly and reversibly acting drugs. In this situation, the measured plasma concentration serves as input for the concentration-effect relationship. The classic and most commonly used pharmacodynamic model under these conditions is the sigmoid $E_{\text{max}}$ model, which is an empirical function for describing nonlinear concentration-effect relationships. It has the general form

$$E = \frac{E_{\text{max}} \cdot C^n}{EC_{50}^n + C^n},$$

Where, the effect $E$ is a function of $E_{\text{max}}$, the maximum effect, $C$, the concentration of the drug; EC50, the concentration of the drug that produces half of the maximal effect; and $n$, the so-called shape factor. The sigmoid $E_{\text{max}}$ model can be related to receptor theory. EC50 is then the parameter characterizing the potency of the drug in the system (i.e., the sensitivity of the organ or tissue to the drug), with $E_{\text{max}}$ reflecting the efficacy (i.e., the maximum response depending on the intrinsic activity of the drug and the number of available receptor sites) [19, 20, 21].

Although $n$ can also be derived from receptor theory as a number of molecules interacting with one receptor, it is in practice merely used to provide a better fit. Albeit the sigmoid $E_{\text{max}}$ model is highly versatile for different situations, several other less complex relationships have been applied under similar conditions (i.e., for direct, reversibly acting drugs with equilibrium between the concentrations at the effect site and in plasma). These models can be seen as specific cases of the sigmoid $E_{\text{max}}$ model and comprise the simple $E_{\text{max}}$ model, the log-linear model, the linear model, and the fixed-effect model [17, 19].

The preferred model in any given situation is determined by many factors, including the drug used the degree of linearity in the concentration-effect curve, and the potential for achieving the maximum effect possible. However, if the defined conditions are not fulfilled (e.g., under non-steady state and for indirectly acting drugs), more sophisticated modeling approaches have to be applied. Other, non-monotonic (e.g., U shaped) relationships have been used for more complex receptor interactions [18].

Kinetic hysteresis analysis has previously been proposed for describing the concentration-time course at extravascular sampling sites, especially for demonstrating changes in the disposition processes affecting antibiotics under pathophysiological conditions [21]. The present paper describes how the area covered by a hysteresis loop can be calculated. With this mathematically derived term, a simple parameter can be used to quantify the amount of
a drug being distributed to an extravascular site. Moreover, a distribution coefficient can be derived, expressing the disposition characteristics of a specific drug.

An anticlockwise hysteresis (Figure. 1) loop occurs when the drug has to be distributed to its site of action. Response for a given plasma concentration is initially low, but increases as the drug is distributed out of the plasma to the site of action. An example is digoxin.

![Anticlockwise Hysteresis](image1)

**Figure 1: An Anticlockwise Hysteresis**

A clockwise hysteresis (Figure. 2) loop occurs when rapid tolerance (tachyphylaxis) develops. The response for a given plasma concentration is initially high, but decreases as tolerance rapidly develops. Examples are cocaine or indirectly acting sympathomimetic drugs such as pseudoephedrine.

![Clockwise Hysteresis](image2)

**Figure 2: A Clockwise Hysteresis**

Since drug concentrations in specific organs cannot be predicted by conventional pharmacokinetic approaches, e. g. stochastic compartment model analysis, experimental assessment has become routine. Tissue specimens are taken from various organs and specific structures, which are often associated with the primary site of infection. In addition, different methods have been elaborated to collect interstitial fluids either from body cavities, or from implanted tissue cages, cotton threads, fibrin clots and etc. Drug concentrations measured at such extravascular sampling sites are routinely reported as absolute values, although it may be difficult to interpret them in terms of disposition characteristics. Therefore, the majority of data are analyzed as ratios of the serum concentration, since there are no straightforward pharmacokinetic models with simultaneous curve fitting of drug concentrations in the serum and at extravascular sampling sites. Distribution into an extravascular body site is a very dynamic and multifactorial process, dependent not only on the time course of drug concentrations in the serum, but also on the biochemical and morphological structure of a specific tissue and its volume. Similar complex processes are found in changes in volume related to pressure, or in concentration-effect profiles of biological mediators or drugs when
followed over time. Hence, kinetic hysteresis analysis has become a meaningful approach in biomedical research for the evaluation of two variables over time [21].

The new field of concentration-effect modelization has been extensively investigated since Sheiner and Holford's studies [17]. This method has been successfully employed both in fundamental human pharmacological research and in the development of new drugs. With respect to the latter, a semantic step forward may be made whereby pharmacological and other writings would gain in precision. In both fields, a fundamental descriptive tool is used: the plot of effect versus drug concentration, with points connected in time order. In many cases, this plot exhibits a counterclockwise loop. If we consider the case of an effect that augments, this means that there is a delay in equilibrium between plasma drug concentration and the concentration of active substance at the effect site. Collapsing the loop requires a complex modelization for determining the virtual concentration at a hypothetical effect site. This loop is called the counterclockwise hysteresis curve, or simply the hysteresis. The word is used in the physical sciences, e.g., magnetism, metallography, rheology, or thermodynamics. It comes from the Greek word (hysteresis) meaning: something which is late, which happens later, refers to a phenomenon where there is a time-lapse between the cause and its effect [22].

**PK/PD MODELING- THE ECONOMIC CONCERNS**

Increasing costs of drug development and reduced pipeline productivity have been growing concerns for new drug development in the recent years. There is a call for use of alternative tools to get answers on efficacy and safety, demonstrated faster with more certainty and at lower cost; pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations is an approach to achieve those objectives [23]. Science of modeling is data driven and it relies on multiple analyses of the same data-set in an iterative mode with successive and/or competing models. It is possible to extrapolate beyond the bounds of the design on which models are defined.

Modeling can add value in all stages of drug development. PK/PD modeling in preclinical phase can enable making internal decisions earlier and easier (e.g. due to better defined critical success factors based on modeling). The greatest cost saving potential of modeling in preclinical phase is in allowing the selection of the optimal drug candidate and abandoning early those which are not predicted to exhibit required efficacy or safety.

PK/PD modeling in early clinical development may enable critical decisions (e.g. go/no go) to be reached earlier based on PK and PD characteristics of the compound, especially if models include comparators data. Abandoning suboptimal compounds early in their development leads to significant cost cutting.

**CONCLUSION**

This review focuses on the pharmacokinetic-pharmacodynamic (PK-PD) modeling strategy adopted during drug discovery and development process. The PK/PD modeling can be used as an ‘applied science’ tool to expedite the process of drug discovery and development with a more scientific and economical approach.

**REFERENCES**


